Improved Synthesis of α-Formylcarboxylic Esters (Commemoration Issue Dedicated to Professor Tatsuo Ooi, On the Occasion of His Retirment)

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Improved Synthesis of α-Formylcarboxylic Esters

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Two improved routes to α-formylcarboxylic esters (**4**) from the corresponding trimethylsilyl ketene acetals (**1**) are described. The $TiCl_4$-catalyzed reaction of **1** with 2-ethoxy-1, 3-oxathiolane affords 2-(1, 3-oxathiolan-2-yl)carboxylic esters (**2**) in good yields which on hydrolsis with chloramine-T trihydrate furnished **4** in almost quantitative yields. The reaction of **1** with ethyl orthoformate in the presence of $TiCl_4$ also furnished **4** in almost quantitative yields in a single step.

KEY WORDS: α-Formylcarboxylic esters/ Trimethylsilyl Ketene acetals/ 2-Ethoxy-1,3-oxathiolane/ 2-(1,3-Oxathiolan-2-yl)carboxylic esters/ Chloramine-T/ Ethyl orthoformate

Recently there has been a considerable interest in the selective α-formylation of carboxylic esters for their use as intermediates. Attempts have occasionally been made for the development of a simple, general and highly selective strategy for the preparation of α-formylcarboxylic esters (**4**), but not much progress could be made. The condensation of carboxylic esters with alkyl formates in the presence of NaH did not find much applicability due to some side reactions.[1] Another approach involving alkylation of 2-carboethoxymethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine followed by the reduction of the oxazine ring and hydrolysis was limited as the starting dihydro-1,3-oxazine derivatives are not easily accessible.[2] There has been reports on the preparation of formylcarboxylic esters from the corresponding α,β-unsaturated carboxylic esters by the cobalt- and rhodium-catalyzed reactions at high pressure. There has been a report recently on the diphosphine-rhodium complex-catalyzed hydroformylation of α,β-unsaturated carboxylic esters at 150°C under 100 atm of synthesis gas.[3] Though high α-selectivity has been achieved in some cases, the β- and γ-formyl derivatives and hydrogenated products are also formed.

We have been interested in the development of a simple, general and high yield methodology for the preparation of **4**. Though our initial efforts were not successful,[4] we have been able to develop a simple method by the reaction of trimethylsilyl ketene acetals (1) with Vilsmeier reagent which gave α-formylated products in moderate yields.[5] We now wish to report in this manuscript two improved methods for the preparation of title compounds. Our approach was based on the synthesis of 2-(1,3-oxathiolan-2-yl)carboxylic esters (**2**) by the reaction of **1** with 2-ethoxy-1,3-oxathiolane in the presence of $TiCl_4$. The reaction proceeded smoothly at room temperature affording **2** in 59–96% yields (Tabel I). Though the regeneration of the

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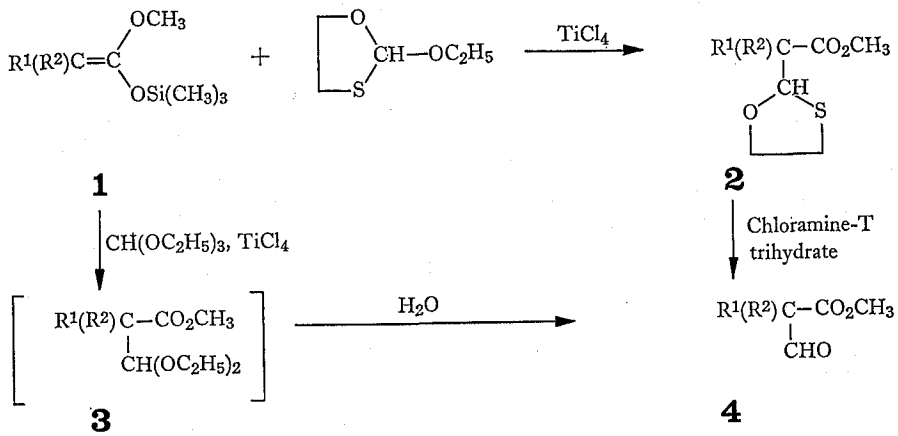
carbonyl compounds by the acid-catalyzed hydrolysis and Raney nickel desulfurization has been reported,[6] the use of chloramine-T trihydrate has proved a better reagent. The hydrolysis of **2** was therefore performed with chloramine-T trihydrate. The tratment of **2d-h** with chloramine-T trihydrate furnished the objective α-formylcarboxylic esters (**4d-h**) in almost quantitative yields. However, treatment of



(**a**) R^1=H, R^2=Et
(**b**) R^1=H, R^2=*n*—Pr
(**c**) R^1=H, R^2=*t*—Bu
(**d**) R^1=R^2=Me
(**e**) R^1=Me, R^2=Et
(**f**) R^1=R^2=Et
(**g**) R^1, R^2=$-(CH_2)_4-$
(**h**) R^1, R^2=$-(CH_2)_5-$

Table I. Preparation of **2**

Starting compund	Product and yield (%)[a]	Physical properties of product	
		Bp (°C/mmHg)	^{1}H-NMR (δ, in $CDCl_3$)
1a	**2a,** 79	73–74 (6)	0.90 (t, 3H), 1.3–1.8 (m, 2H), 2.2–2.7 (m, 1H, 2.8–3.3 (m, 2H), 3.70 (s, 3H), 3.8–4.4 (m, 2H) and 4.99 and 5.08 (d and d, 1H)
1b	**2b,** 91	75–76 (5)	0.8–1.2 (m, 5H), 1.6–2.3 (m, 2H), 2.3–2.7 (m, 2H), 2.8–3.2 (m, 2H), 3.75 (s, 3H), 4.0–4.4 (m, 2H) and 5.29 and 5.32 (d and d, 1H)
1c	**2c,** 81	Not measured	1.06 (s, 9H), 2.51 (d, 1H), 2.8–3.1 (m, 2H), 3.62 (s, 3H), 4.0–4.4 (m, 2H) and 5.10 and 5.37 (d and d, 1H)
1d	**2d,** 96	74–76 (5)	1.14 (s, 3H), 1.22 (s, 3H), 2.7–3.0 (m, 2H), 3.76 (s, 3H), 4.2–4.6 (m, 2H) and 5.30 (s, 1H)
1e	**2e,** 68	Not measured	0.80 (t, 3H), 1.11 (s, 3H), 1.4–1.8 (m, 2H), 2.5–2.8 (m, 2H), 3.47 (s, 3H), 4.0–4.4 (m, 2H) and 5.12 (s, 1H)
1f	**2f,** 59	77–78 (3)	0.92 (t, 6H), 1.5–2.0 (m, 4H), 2.7–3.0 (m, 2H), 3.74 (s, 3H), 4.2–4.6 (m, 2H) and 5.40 (s, 1H)
1g	**2g,** 76	84–85 (0.4)	1.5–2.3 (m, 8H), 2.7–3.2 (m, 2H), 3.72 (s, 3H), 4.2–4.6 (m, 2H) and 5.64 (s, 1H)
1h	**2h,** 67	96–97 (0.5)	1.0–2.4 (m, 10H), 2,8–3.2 (m, 2H), 3.78 (s, 3H), 4.2–4.6 (m, 2H) and 5.21 (s, 1H)

a) Isolated yield by column chromatography.

2a-c did not yield the expected products. It is not clear how the presence of a hydrogen at α-position affects the hydrolytic step so drastically. The compounds **2** have not been previously reported and were characterized by spectral methods. The formation of **2** can be explained by the electrophilic attack of the 1,3-oxathiolan-2-ium ion on the **1** releasing trimethylsilyl group. The conversion of **2** to **4** can be explained via the formation of an unstable sulfilimine and zwitter ion.[6]

In search of a more general method, we investigated the reaction of **1** with ethyl orthoformate in the presence of $TiCl_4$. The $TiCl_4$-catalyzed direct formylation of **1** with a slight excess of ethyl orthoformate in dichloromethane at room temperature proceeded smoothly and the objective **4** were obtained in almost quantitative yields (Tabel III). The formation of **4** from **1** by the $TiCl_4$-catalyzed reaction with ethyl orthoformate can also be explained by an analogous route as in the previous case.

Table II. Conversion of **2** into **4**

Starting compound	Product and yield (%)[a]	Physical properties of product: Bp (°C/mmHg)	Physical properties of product: ^{1}HNMR (δ, in $CDCl_3$)
2d	**4d**, 75	48 (17) [lit.[4] 50–53 (16)]	1.34 (s, 6H), 3.74 (s, 3H) and 9.61 (s, 1H)
2e	**4e**, 90	72–74 (20) [lit.[4] 65–66 (17.5)]	0.88 (t, 3H), 1.31 (s, 3H), 1.6–2.1 (m, 2H), 3.80 (s, 3H) and 9.69 (s, 1H)
2f	**4f**, 94	72 (10–12) [lit.[7] 140 (38)][b]	0.88 (t, 6H), 1.88 (q, 4H), 3.82 (s, 3H) and 9.81 (s, 1H)
2g	**4g**, 96	89 (17) [lit.[4] 92–93 (17.5)]	1.4–2.3 (m, 8H), 3.76 (s, 3H) and 9.59 (s, 1H)
2h	**4h**, 94	104 (18) [lit.[4] 62–63 (2.5)]	1.1–2.2 (m, 10H), 3.77 (s, 3H) and 9.48 (s, 1H)

a) Isolated yield by column chromatography.
b) This value refers to the bath temperature in a bulb-to-bulb distillation.

Table III. One-step Synthesis of **4** with Ethyl Orthoformate

Starting compound	Product and yield (%)[a]	Physical properties of product: Bp (°C/mmHg)	Physical properties of product: ^{1}H-NMR (δ, in $CDCl_3$)[b]
1a	**4a**, 85	55 (17) [lit.[3] 43–46 (10)]	Ketonic form: 0.98 (t, 3H), 1.5–2.4 (m, 2H), 3.0–3.4 (m, 1H), 3.29 (s, 3H) and 9.68 (d, 1H) Enolic form: 1.02 (t, 3H), 1.5–2.4(m, 2H), 3.29 (s, 3H), 6.87 (d, 1H) and 11.30 (d, 1H)
1d	**4d**, 87		
1e	**4e**, 78		
1f	**4f**, 94	See Table II.	
1g	**4g**, 98		
1h	**4h**, 95		

a) Isolated yield by column chromatography.
b) The following was confirmed from the ^{1}H-NMR spectral data: The compound **4a** consisted initially of the ketonic form, but it gradually changed to an equilibrium mixture containing approximately half of the enolic form.

The attack by the diethoxycarbonium ion on **1** releasing trimethylsilyl cation seems to give intermediate **3** which are hydrolyzed during aqueous work-up.

The present results indicate that two new methods are now available for the preparation of **4** selectively. The existence of these methods in addition to previously known methods make the compounds **4** more easily accessible.

EXPERIMENTAL

Preparation of 2-(1,3-Oxathiolan-2-yl)carboxylic Esters (2) and Their Hydrolysis into α-Formylcarboxylic Esters (4). To a cooled (−78°C) solution containing 1.0 mmol of one of **1** and 1.1 mmol (0.15 g) of 2-ethoxy-1,3-oxathiolane in 10 ml of dichloromethane was added during 5 min 1.1 mmol (0.21 g) of $TiCl_4$. The reaction mixture was allowed to warm to room temperature and stirred for 2 h at that temperature, and then treated with 20 ml of aqueous $NaHCO_3$. The organic layer was separated and combined with ethereal extracts (20 ml×2) of the aqueous phase. It was dried over $MgSO_4$ and concentrated under reduced pressure to afford a residue which was purified by column chromatography (silica gel, 10% ethyl acetate-hexane as an eluent) to give either one of **2**. To a suspension of 2.0 mmol (0.57 g) of chloramine-T trihydrate in 10 ml of water was added at room temperature during 5 min 1.0 mmol of one of **2** above-mentioned. The reaction mixture was stirred at that temperature during 15–30 min, and then treated with 20–30 ml of carbon tetrachloride. The resulting precipitate was collected on a filter and washed with carbon tetrachloride (10 ml×2). The organic layer of the filtrate was combined with the washings, dried over $MgSO_4$, and concentrated under reduced pressure to afford a residue which was subjected to column chromatography (silica gel, 40% ethyl acetate-hexane as an eluent) to give the corresponding **4**.

One-step Conversion of Trimethylsilyl Ketene Acetals (1) into α-Formylcarboxylic Esters (4). To a cooled (−78°C) solution containing 1.0 mmol of one of **1** and 1.1 mmol (0.17 g) of ethyl orthoformate in 10 ml of dichloromethane was added during 5 min 1.1 mmol (0.21 g) of $TiCl_4$. The reaction mixture was allowed to warm to room temperature and stirred for 1–3 h at that temperature, and then treated with 20 ml of aqueous $NaHCO_3$. The organic layer was combined with ethereal extracts (20 ml×3) of the aqueous phase, dried over $MgSO_4$, and concentrated under reduced pressure to afford a crude product which was purified similarly as above.

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